UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,736	07/19/2007	Sophie Lotersztajn	C0300.0022	9624

32172 7590 08/17/2009

DICKSTEIN SHAPIRO LLP
1633 Broadway
NEW YORK, NY 10019

EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
08/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/598,736	LOTERSZTAJN ET AL.	
	Examiner	Art Unit	
	Brian-Yong S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicants Response to Election of Species Requirement Acknowledged

1. Applicants' election with N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide and alcoholic liver cirrhosis is acknowledged. Applicant made this election with traverse. Claims 2, 15, 17, 18, 19, 21, 23 and 27 read on the elected invention.

Applicants traverse the restriction requirement on the grounds that when making a lack of unity of invention requirement, the Office must list the different groups of claims and explain why each group lacks unity with each other group. Applicant allege that the requirement of unity of invention is fulfilled, as the claims all relate to CB1 antagonists and all the recited diseases, namely liver fibrosis, are treatable by a CB1 antagonist, and that the Office withdraw the election/restriction requirement.

This argument is not persuasive, as species of the instant invention (more than one species of the generic invention) lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1. The technical feature linking the invention, namely CB1 antagonist for the treatment of hepatic disease, e.g., cirrhosis of the liver and hepatic failure, is known in the art (see US 5939429; WO 2003/084943; WO 03/084930; WO 03/063781; WO 03/087037; Gabbay E. et al., "Treatment with an endocannabinoid antagonist imprves neurological function and survival in an animal model of fulminant hepatic failure, Hepatology, vol. 38, No. 4, Suppl. 1, 2003, page 541A; Batkai et al., "Endocannabinoids acting at vascular CB1 receptors mediate the vasodilated state in advanced liver cirrhosis", Nature Medicine, vol. 7, no. 7, 2001, pages 827-832). Furthermore, the compounds of the formula II is known in the art (see EP 656354-A1 which is English equivalent to US 5624941) and the species recited in claim 12 and claim 18 respectively are distinct species which have

different chemical or physical properties. Therefore, the technical feature linking the inventions does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art. These species are not linked by the same or a corresponding special technical feature as to form a single general inventive concept.

In addition, the search of the entire groups of species in the patent and/or non-patent literature (a significant part of a thorough examination) would be burdensome. Therefore, the requirement is still deemed proper, and made Final. Claims 12-14, 20, 22 and 24-26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims.

2. In response to applicant's statement that the election/restriction requirement incorrectly identify that there are claims to product and process, the examiner recognizes the inadvertent error of including such statement in pages 3-4 of the election/restriction requirement mailed 05/14/09. According, the examiner vacates such statements from the previous O.A.

3. Claims 2, 15, 17, 18, 19, 21, 23 and 27 are currently pending for prosecution on the merits.

Information Disclosure Statement

4. Enclosed is an initialed copy of PTO 1449 which has been considered for your records.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 2, 17 and 22-27 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12, 15-17, 19 and 21-24 are directed to encompass "CB1 receptor antagonist" which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these meet the written description provision of 35 USC 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompasses a myriad of possibilities. To the extent that no structure function data is disclosed in connection with theses functionally described compounds to correlate, or there is not disclosed correlation established between these functional drugs and the contemplated desired therapeutic effect to be achieved in practicing the instant invention, the specification provides insufficient written description to support the genus encompassed by the claims.

Vas-Cath Inc. Mahurkar, 19 USPQ2d 1111, makes clear the "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of CB1 receptor antagonist represented by the formula II, the skilled artisan cannot envision the detailed chemical structure of the encompassed generic CB1 receptor

antagonist, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

…To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966(1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)* ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 2, 15, 17, 18, 19, 21, 23 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toupence et al. (US 7091216), and further in view of Shakkebaek et al. (US 5492891).

Toupenece teaches a use of cannabinoid-1 (CB1) receptor antagonist, namely compound of the formula 1, for the treatment of disease mediated by the CB1 receptor including cirrhosis of the liver and substance abuse disorder (e.g., alcoholism). See abstract; column 2, lines 51-53; column 3, line 3. Toupenece discloses rimonabant as known CB1 receptor antagonist (column 47, lines 31-36) among therapeutic agents that are suitable for the practice of invention. The teaching of Toupenece differs from the claimed invention because rimonabant is not specifically named for the treatment of alcoholic liver cirrhosis.

Shakkebaek is being provided as a supplemental reference to demonstrate nexus between alcoholic abuse and cirrhosis of liver development. (column 1, lines 10-32).

However, one having ordinary skill in the art would have expected as taught by Toupenece that compounds having CB1 receptor antagonist activity would be useful in the treatment of cirrhosis of the liver as well as to treatment of alcoholism or alcohol addiction. One having ordinary skill in the art would have reasonable expectation of success per view of Toupenece and Shakkebaek combination that compounds having CB1 receptor antagonist activity would be useful in the treatment of cirrhosis of the liver induced by alcoholism or alcohol addiction. Furthermore, one having ordinary skill in the art would have expected that other known CB1 receptor antagonist mentioned in Toupenece, namely rimonabant, would provide similar activity as the formula 1 compounds. One having ordinary skill in the art would have been motivated to extend the usage of other known CB1 receptor antagonist such as rimonabant to patient suffering from cirrhosis of the liver or alcohol addiction or cirrhosis of the liver coextensive with alcohol addiction or resulted from alcohol abuse.

With respect to the specific dosage amounts of CB1 receptor antagonist recited in claims 15 and 27, those of ordinary skill in the art would have been readily optimized effective dosage amounts as determined by good medical practice and the clinical condition of the individual patient. One having ordinary skilled in the art would have been motivated to make such modification to extend the usage of said composition in oral dosage forms, particularly solid dosage form, to accommodate patient's preference and needs where the compliance could be improved with effective and well tolerated drug.

Regardless of the manner of administration, the specific dose would have been calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation. Furthermore, the final dosage regimen would have been determined by the attending physician, considering the drug's specific activity, the responsiveness of the subject, the age, condition, body weight and diet, the severity of any infection, time of administration and other clinical factors. Given the teachings in the state of art, those of ordinary skill would be able to determine appropriate dosage amounts of the CB1 receptor antagonist having optimum therapeutic index, and would be motivated to determine optimum amounts to maximize the efficacy of drugs.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 2, 15, 17, 18, 19, 21, 23 and 27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 3 of U.S. Patent No. 7320805.

Although the conflicting claims are not identical, they are not patentably distinct from each. Both of the instant application and the patent are drawn to a method of treating a disease of liver administering a composition comprising CB1 receptor antagonist to a patient having the disease, namely alcoholic liver cirrhosis.

Although the instant N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide is not specifically named as the CB1 receptor antagonist in the referenced claim 3, one having ordinary skill in the art, reading the disclosure (column 12, line 45 through column 13, line 40) of the patent, would have at once envisage N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide from the limited preferred species of CB1 receptor antagonist. As discussed in preceding comments, the examiner determines that one of ordinary skill in the art would at once envisage the subject matter within claim 3 of the reference.

It is noted that the transitional term "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. Thus, the referenced composition comprising CB2 receptor agonist and CB1 receptor antagonist makes obvious the instant invention.

With respect to the specific dosage amounts of CB1 receptor antagonist recited in claims 15 and 27, those of ordinary skill in the art would have been readily optimized effective dosage amounts as determined by good medical practice and the clinical condition of the individual patient. One having ordinary skilled in the art would have been motivated to make such modification to extend the usage of said composition in oral dosage forms, particularly solid

dosage form, to accommodate patient's preference and needs where the compliance could be improved with effective and well tolerated drug.

Regardless of the manner of administration, the specific dose would have been calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation. Furthermore, the final dosage regimen would have been determined by the attending physician, considering the drug's specific activity, the responsiveness of the subject, the age, condition, body weight and diet, the severity of any infection, time of administration and other clinical factors. Given the teachings in the state of art, those of ordinary skill would be able to determine appropriate dosage amounts of the CB1 receptor antagonist having optimum therapeutic index, and would be motivated to determine optimum amounts to maximize the efficacy of drugs.

Conclusion

8. No Claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614